

Peripartum Cardiomyopathy

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Introduction

Peripartum cardiomyopathy is an uncommon form of congestive heart failure. Since its discovery much has been learned about this disease process, and now better treatment options exist. Obstetricians and family physicians should be familiar with this disorder because they will be the first medical contact for these patients. In this article we have reviewed the current literature and have placed special emphasis on the current treatment strategies. The early diagnosis and institution of medical treatment for this cardiomyopathy is critical because it may affect the patient's long-term prognosis.

A relationship between pregnancy and dilated cardiomyopathy was first noted in 1870 when Virchow and Porak first reported autopsy evidence of myocardial degeneration in patients who died in the puerperium¹. In 1937 Gouley et al.² described the clinical and pathologic features of seven pregnant patients who had severe and often fatal heart failure. These women had a dilated, nonischemic cardiomyopathy in the later months of their pregnancies, which persisted after delivery. Four of the seven patients died; the autopsy demonstrated enlarged hearts with widespread severe focal areas of necrosis and fibrosis. These findings were atypical compared with those of other patients with myocardial failure. Therefore the authors proposed that this heart failure was related to pregnancy and the puerperium either directly or indirectly.

Since these reports this disorder has been referred to as toxic postpartum heart disease, postpartum heart failure, postpartum myocarditis, and postpartum heart disease; however, today most physicians refer to this disease as peripartum cardiomyopathy¹.

Incidence and etiology

Peripartum cardiomyopathy occurs in one out of every 3000 to 15,000 pregnancies, with a higher incidence in Africa^{3,4}. In spite of the higher incidence in Africans, all races can be affected. Women at particular risk are older, multiparous, and having twin births^{4,5}. Given the approximate 4

million annual deliveries in the United States, it can be estimated that 250 to 1350 women will have peripartum cardiomyopathy each year⁶.

The etiology of postpartum cardiomyopathy is currently unknown. Early evidence had suggested that nutritional deficiencies may play a role because studies noted an increased incidence of peripartum cardiomyopathy in women who were malnourished. However, more recent studies do not support this relationship^{3,7,8}. Currently, more and more evidence suggests that peripartum cardiomyopathy is actually a type of myocarditis arising from an infectious, autoimmune, or idiopathic process.

Some studies suggest that the etiology may be the result of myocarditis. The relationship between pregnancy and viral myocarditis was first published in 1968. Animal studies demonstrated that pregnant mice are more susceptible to viral infections than nonpregnant ones are⁹. Furthermore, studies by Farbor and Glasgow demonstrated that these viruses multiply to a greater level in the hearts of pregnant mice. This observance may be the result of higher levels of adrenal corticosteroids and "blocking antibodies" formed during normal pregnancy, which leads to a "relative immunosuppression"^{9,10}. This higher viral concentration in the myocardium has been associated with myocarditis by histologic diagnosis¹⁰. Further studies have demonstrated that, when cardiac output rises (which occurs with normal pregnancy), myocardial viral lesions worsen¹¹.

Additionally, numerous studies have reported histologic evidence of myocarditis in endomyocardial biopsy samples obtained from patients with peripartum cardiomyopathy. This incidence varies in the literature ranging from 8.8% to 100%¹²⁻¹⁴. Midei et al.¹³ performed endomyocardial biopsy on 18 patients with peripartum cardiomyopathy, of which 14 specimens were positive for myocarditis. Melvin et al.¹³ reported another 3 patients with peripartum cardiomyopathy and biopsy-proved myocarditis. Coincident with the clinical improvement, follow-up endomyocardial biopsy specimens revealed resolution of the myocarditis.

Timing of the biopsy may be important. Biopsy specimens in the study by Midei et al.¹³ were obtained a mean of 33 ± 9 days from the onset of symptoms. Other groups obtained biopsy specimens within 1 week from the onset of symptoms^{8,13}. Midei et al.¹² note that there is a

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subset of patients who have a rapid, spontaneous improvement and recommend that endomyocardial biopsy be reserved for those patients who do not improve within 1 week of onset of symptoms. Unfortunately, in spite of the implication of these reports, the endomyocardial biopsy cannot always be relied on to make the diagnosis of myocarditis. The difficulty lies in the high rate of false-negative results because of the focal nature of the inflammatory infiltrates. In patients with autopsy-proved myocarditis, the diagnosis could be made by pre-mortem endomyocardial biopsy in only 63%¹⁵.

Other investigators have suggested that the etiology is due to an autoimmune process. In one report evaluation of a patient who had congestive heart failure after delivery revealed that all laboratory values were normal, including antibody titers to various viruses. However, the patient did have antibodies to smooth muscle and actin. The authors postulate that after delivery the fast degeneration of the uterus results in fragmentation of tropocollagen by collagenolytic enzymes releasing actin, myosin, and their metabolites. Antibodies are formed against actin that cross-react with the myocardium, and the patient subsequently has a cardiomyopathy¹⁶. No other studies examined the formation of antibodies to actin as the primary etiology of peripartum cardiomyopathy.

Recently, an association between tocolytic therapy and peripartum cardiomyopathy has been reported¹⁷ in this case study of 15 women with peripartum cardiomyopathy, 4 had received prolonged terbutaline therapy. It is unclear, however, whether these agents actually induce a cardiomyopathy or simply unmask subclinical heart disease. Regardless, clinicians should perform frequent cardiovascular examination on patients receiving tocolytic therapy.

From the current data the etiology of peripartum cardiomyopathy remains unclear. However, there is compelling data from animal and human studies suggesting the cardiomyopathy may be caused by some form of myocarditis.

Diagnosis

The criteria for the diagnosis of peripartum cardiomyopathy were established by Demakis et al.¹⁸ in 1971. The heart failure must become manifest in the last month of pregnancy or within 5 months of the delivery and no other etiology for the heart failure can be found.

Diagnostic criteria for peripartum cardiomyopathy

1. Evidence of left ventricular dysfunction (i.e., left ventricular ejection fraction <45%).
2. Heart failure symptoms become manifest in last month of pregnancy or within 5 months of delivery.
3. No other etiology for the heart failure is established.

The clinician must be careful to exclude other causes of heart disease before making the diagnosis of peripartum cardiomyopathy, which can be challenging. During pregnancy there are many physiologic changes that can mimic heart failure. In the first trimester there is an increase in blood volume, which may result in jugular venous distention. In the later months of a normal pregnancy pedal edema is often noted. Dyspnea and fatigue are also common symptoms¹⁹. These normal physiologic changes may unmask subclinical or compensated heart disease for the first time. For example, as the patient's fluid status increases, asymptomatic valvular heart disease may become symptomatic for the first time.

Therefore, in patients with suspected left ventricular dysfunction, echocardiography is recommended not only to assist in making the diagnosis but also to exclude other etiologies of heart failure such as valvular heart disease.

The presentation of patients with peripartum cardiomyopathy is similar to that of other patients with systolic left ventricular dysfunction. Usual presenting complaints consist of chest pain, dyspnea on exertion, orthopnea, cough, paroxysmal nocturnal dyspnea, pedal edema, or fatigue. As shown in Table II, physical examination can be significant for signs of right and left heart failure^{1, 5, 7, 18}.

The electrocardiogram usually demonstrates a normal sinus or sinus tachycardia rhythm, but frequent ectopy and other atrial arrhythmias may also be present^{1, 5, 7, 18}. Left ventricular hypertrophy, inverted T waves, Q waves, and nonspecific ST-T changes have also been reported. All patients usually exhibit cardiomegaly on the chest x-ray film^{7, 18}.

Presenting features of peripartum cardiomyopathy**Symptoms**

1. Dyspnea.
2. Orthopnea.
3. Paroxysmal nocturnal dyspnea.
4. Cough.
5. Chest pain.
6. Anorexia.
7. Fatigue.
8. Pedal edema.

Signs**General**

1. Jugular venous distention.
2. Tachycardia.
3. Tachypnea.
4. Hepatomegaly.
5. Hepatojugular reflux.
6. Ascites.
7. Peripheral edema.
8. Mental status changes.
9. Thromboemboli.

Cardiac

10. Gallop rhythm.
11. Mitral regurgitation murmur.
12. Loud P2.
13. Rales.

Treatment

The treatment for peripartum cardiomyopathy is similar to that for other nonischemic dilated cardiomyopathies; however, consideration must also be given for the fetus.

Treatment of peripartum cardiomyopathy**Nonpharmaceutical therapy**

- Low sodium diet (<4 gm/day).
- Fluid restriction (<2 L/day).
- Modest daily exercise (i.e., walking).

Oral pharmaceutical therapy

A) Prepartum.

1. Amlodipine.
2. Hydralazine/nitrates.
3. Digoxin.
4. Diuretics.
5. β -Blockers.

B) Post partum.

1. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.
2. Digoxin.
3. Diuretics.
4. Amlodipine.

5. Hydralazine/nitrates.
6. β -Blockers.

Intravenous pharmaceutical therapy for patients with severe symptoms

- Unresponsive to above oral therapy.
- Dobutamine.
- Dopamine.
- Milrinone.
- Nitroprusside.

In general, the goal is to reduce to amount of volume returning to the heart (preload reduction), decrease the resistance against which the heart must pump (afterload reduction), and increase the contractile force of the heart (inotropy).

The cornerstone of optimal outpatient oral pharmacologic therapy for cardiomyopathy begins with afterload reduction with use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers^{20, 22}. Unfortunately, pregnancy is a contraindication to the use of angiotensin-converting enzyme inhibitors²³ and likely the angiotensin receptor blockers as well. In this circumstance, the combination of hydralazine and nitroglycerin or amlodipine can be safely used in pregnancy to provide needed afterload reduction^{24, 25}. Preload reduction can be accomplished with diuretics and low-dose oral nitrates. In pregnancy diuretics must be used with caution as to avoid dehydration.

Oral inotropic therapy is provided by digoxin^{26, 27}. Furthermore, the deleterious effects of excessive sympathetic nervous system activation may be blocked and reversed with low-dose β -blockers^{28, 29}. The long-term use of β -blockers during pregnancy may be associated with low-birth-weight (LBW) babies; therefore care should be given when these agents are used prepartum³⁰.

Together these drugs work to improve the patient's hemodynamic parameters and congestive symptoms. Afterload reduction therapy and sympathetic blockade therapy have been shown to improve long-term patient survival.^{20, 21, 28}

Suggested treatment regimen for the patient with peripartum cardiomyopathy

1. In postpartum patients institute ACE inhibitor therapy with enalapril 5 mg twice daily and titrate up to a maximum dose of 20 mg twice daily, yet maintain systolic blood pressure approximately 100 to 110 mm Hg. In prepartum patients use vasodilator such as amlodipine 5 mg once daily titrating to 10 mg once daily or combination of hydralazine 25 to 100 mg four times daily and long-acting

- nitroglycerin, to lower systolic blood pressure to 100 to 110 mm Hg.
2. Start digoxin to achieve a serum level of 1 to 2 ng/dl.
 3. Start diuretic therapy (furosemide 20 to 40 mg once daily) to control symptoms related to volume excess. Use with caution in prepartum patients.
 4. In postpartum patient start low-dose β -blocker therapy (i.e., metoprolol 12.5 mg twice daily) and titrate for heart rate 80 to 100 beats/min. Use with caution in prepartum patients.
 5. Add additional vasodilator agents as needed to control systemic blood pressure (e.g., goal is systolic blood pressure 110 mm Hg).
 6. Monitor ambulation for 24 to 48 hours.
 7. Dietary consultation for fluid-restricted, low-salt diet.
 8. Detailed patient education and counseling.
 9. Referral to exercise rehabilitation program.
 10. Vigilant follow-up to include measure of cardiac function within 3 to 6 months of treatment onset.

In the treatment of acutely ill or highly symptomatic patients, intravenous preload and afterload reducing agents (nitroprusside, nitroglycerin) or inotropic agents (dobutamine, dopamine, milrinone) should be considered. Intravenous nitroglycerin, dobutamine, dopamine, and milrinone can be used in pregnant patients if medically necessary. Nitroprusside can be used to further optimize hemodynamics and clinical condition; however, the risks and benefits of nitroprusside therapy should be considered because thiocyanate and cyanide may accumulate in the fetus³¹. Invasive hemodynamic monitoring is often used to guide the acute phase of this therapy.

Past hemodynamic studies performed in patients with normal pregnancies between 36 and 38 weeks' gestation document a pulse rate of 83 beats/min, right atrial pressure of 4 mm Hg, pulmonary capillary wedge pressure of 8 mm Hg, cardiac output of 6 L/min, mean arterial pressure (MAP) of 90 mm Hg, and systemic vascular resistance of 1210 dynes/sec/cm. When repeated again 11 to 13 weeks post partum there is a fall in the cardiac output to 4.3 L/min and pulse rate to 71 beats/min and an increase in systemic vascular resistance to 1530 dynes/sec/cm. There is no appreciable change in the right atrial pressure, pulmonary capillary wedge pressure, or MAP³². On the basis of these data, the hemodynamic goals for the patient with peripartum cardiomyopathy would be an MAP of approximately 75 mm Hg,

heart rate between 60 and 80 beats/min, systemic vascular resistance between 800 and 1200 dynes/sec/cm, pulmonary capillary wedge pressure between 16 and 20 mm/Hg, and a cardiac index >2.5 L/min/m². It would be advisable to have a cardiologist or intensivist assist in this management.

There is a high incidence in thromboembolism in this population. These observations were noted before initiation of mandatory bed rest, which was the standard of care in the past^{7,18}. Thrombi are the result of the hypercoagulable state of pregnancy and of stasis and turbulent flow in the dilated heart. Therefore anticoagulation with subcutaneous heparin (i.e., 5000 units heparin subcutaneously twice daily) should be strongly considered in this population. Warfarin (Coumadin), on the other hand, should be avoided during pregnancy because it can cause birth defects³³.

With the increasing evidence that peripartum cardiomyopathy may be the result of myocarditis, immunosuppressive therapy may be an important treatment option. Melvin et al.¹³ reported that 3 patients with peripartum cardiomyopathy and biopsy-proved myocarditis improved with immunosuppression. Midei et al.¹² studied 14 patients with peripartum cardiomyopathy and biopsy-proved myocarditis. 10 patients received immunosuppressive therapy; 9 had symptomatic improvement. However, the other four patients with myocarditis not treated with immunosuppressive agents also exhibited a similar degree of improvement. If the endomyocardial biopsy specimen demonstrates myocarditis, immunosuppressive therapy can be considered. However, a prospective, blinded study is needed to help further define the role for immunosuppressive agents.

Non-pharmacologic treatments include sodium restriction, fluid restriction, and modest exercise. These dietary restrictions are very important. The best medical regimen can be defeated by dietary indiscretion. The daily intake of sodium should not exceed 4 gm, and the daily intake of fluids should not exceed 2 L. Further restriction of both sodium and fluid intake may be required for some patients. Exercise, such as walking and bicycling, have been proved to increase the exercise capacity and improve survival in patients with congestive heart failure. It would be best if these patients were referred to a formal cardiac rehabilitation program; however, if one is not available or if the referral is not possible, consider having the patient walk or bike approximately 1 mile daily.

Cardiac transplantation offers a final yet very viable alternative for patients with peripartum cardiomyopathy who do not improve or who continue to deteriorate with medical management.

Because donor hearts are usually not readily available, it may become necessary to support the patient with an intraaortic balloon pump or ventricular assist device as a bridge to transplant.

Natural history

Too few patients with peripartum cardiomyopathy have been studied to fully analyze the natural history of this disease. Furthermore, early studies were performed before the development of echocardiography, and some patients may have had other causes for their heart disease.

Demakis et al.¹⁸ divided a group of 27 patients into two groups at 6 months on the basis of a normal or enlarged heart size. There was no difference in the age of the patient, time of onset of symptoms, or initial therapy. 14 of 27, or 52%, had resolution of the cardiomegaly, and none of these patients died from congestive heart failure. However, in the patients with persistent cardiomegaly 11 of 13, or 85%, died of heart failure, surviving an average of 4.7 years¹⁸.

Therefore, if the congestive cardiomyopathy persists after 6 months, it is likely irreversible and associated with a worse survival.

O'Connell et al.⁸ also confirmed that 50% of the patients had spontaneous resolution of their symptoms. The unfortunate 50% of patients whose cardiomyopathy does not resolve have a high mortality rate. Data from the study of Midei et al.¹² from the 1980s report that only 1 of 14 patients with peripartum cardiomyopathy died and that 2 of 14 received a transplant; therefore the mortality rate was only 7%. This lower mortality may be attributed to the use of better medical treatment for heart failure or cardiac transplantation. However, a recently published study of 28 patients from 1986 to 1994 demonstrated a poorer prognosis; 5 of the 28 patients died, 3 received a heart transplant, and only 2 patients recovered. Therefore 93% of patients had progressive or persistent cardiomyopathy. It is difficult to interpret these results because many of these patients had associated comorbid disorders such as hypertension and past anthracycline chemotherapy use, and no assessment of left ventricular function before pregnancy was available³⁴.

Survivors of peripartum cardiomyopathy have been compared with nonsurvivors. The survivors had a significantly higher left ventricular ejection fraction (22.8% vs 10.6%) and a smaller left ventricular end-diastolic diameter (5.8 vs 6.9 cm) at the time of diagnosis compared with the nonsurvivors. There was no difference in the pulmonary arterial pressure, pulmonary capillary wedge pressure, and cardiac index.⁸ Prognostic

studies also suggest that patients who have symptoms >2 weeks post partum have a poorer prognosis. This suggests that this disorder may indeed have different etiologies. There also is a trend for a poorer prognosis in women who are black, multiparous, and >30 years old³⁵.

There is concern that patients with peripartum cardiomyopathy are at risk for recurrence of their cardiomyopathy with future pregnancies. From a group of 14 patients whose peripartum cardiomyopathy had resolved by 6 months, 8 patients had subsequent pregnancies¹⁸. Of these, 2 had recurrent cardiomyopathy and congestive symptoms. However, both patients had only a temporary deterioration. From the group of the patients with persistent cardiomyopathy, 6 had subsequent pregnancies. Three had worsening symptoms eventually resulting in death. Furthermore, a report of 4 peripartum cardiomyopathy patients who had resolution of their left ventricular dysfunction revealed no increased risk for cardiac problems on the subsequent pregnancies³⁶. These findings are also supported by another study in which patients who had full recovery from their peripartum cardiomyopathy had a successful pregnancy without recurrence of heart failure symptoms. On the other hand, there were 5 pregnancies in the group of patients who did not recover, 4 of whom had an exacerbation of heart failure³⁴.

Even those who have functional recovery may not have total recovery of cardiac function. Lampert et al.³⁷ found that women who have recovery from peripartum cardiomyopathy by regaining normal resting left ventricular size and function may still have decreased contractile reserve when placed under hemodynamic stress. Therefore women with peripartum cardiomyopathy need extensive counseling about future pregnancies and the risk for recurrence of cardiomyopathy and death. Because the data show that patients with persistent peripartum cardiomyopathy have a high morbidity and mortality rate, some authors suggest that these patients should avoid subsequent pregnancies¹⁸. In the patients with resolution of the symptoms, counseling is still recommended regarding the risk of recurrence in future pregnancies.

As may be expected, the cardiomyopathy can also affect the fetus. In the study by Witlin et al.³⁴ there were no fetal deaths, but there was an increased incidence of premature and LBW infants. These findings suggest that the underlying disease process may begin much earlier than the clinical signs and symptoms are manifested. The development of peripartum cardiomyopathy in the mother may be a marker of high risk for the baby.

Comment

Peripartum cardiomyopathy is an unusual form of dilated cardiomyopathy that is often fatal and strikes in the prime of a young woman's life.

Because there is much variation in the course of the disease, there is also a lack of good data regarding the etiology (or etiologies) of peripartum cardiomyopathy. Although evidence suggests peripartum cardiomyopathy may be the result of a form of myocarditis, there is controversy whether this disease is related to a viral illness or an autoimmune disease of pregnancy.

When a pregnant patient has symptoms of heart failure, it is important to pursue the etiology because some may have ischemic or valvular heart disease.

For those patients with peripartum cardiomyopathy, there seems to be a trend toward improved survival and functional capacity that may be related to improved and more aggressive medical management. Prospective, double-blinded trials involving immunosuppression drugs are needed to help clarify the issue of whether immunosuppression is helpful in these patients. To date, use of these drugs for this illness is controversial.

For those who do not improve with conventional medical therapy, have persistent cardiomegaly, or have moderate to severe mitral regurgitation, referral to a cardiac transplant center should be considered.

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